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Immunomodulatory, anti-inflammatory, and antioxidant effects of curcumin

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ABSTRACT

Turmeric is a widely used spice derived from the rhizomes of Curcuma longa. Having been used as a dietary spice, it has drawn scientists' attention to the possible medicinal benefits of its active compounds called curcuminoids which consist of curcumin, demethoxycurcumin and bisdemethoxycurcmin. Considering wide range of pharmacological properties that curcumin offers, numerous studies have investigated its potency as a therapeutic agent in various diseases such as autoimmune, cardiovascular, neoplastic, pulmonary, neurodegenerative and metabolic diseases. With regard to its wide array of health benefits and published data on the underlying mechanisms of its action, a complex interaction between three main events including inflammation, oxidative stress, and immunity, seems to contribute to different therapeutic roles of this compound. Hence, this review discusses the current knowledge on the anti-inflammatory, antioxidant, and immunomodulatory roles of curcumin with the hope of recruiting curcumin as a therapeutic agent in future therapeutic regimen in order to enhance the efficacy of the treatment, as well as decreasing the adverse effects of synthetic chemical drugs.

Implication for health policy/practice/research/medical education:
This review revealed that curcumin treatment can be considered as a supplementary remedy for prevention of oxidative stress, inflammation, and immunomodulatory disorders. The literatures support the candidacy of this compound as a possible prospective natural drug and raise the possibility of recruiting curcumin in future therapeutic regimens.

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Introduction

Turmeric is a widely used spice derived from the rhizomes of *Curcuma longa* which belongs to the ginger family (1). Having been used as a dietary spice, it has drawn scientists' attention to the possible medicinal benefits of its active compounds called curcuminoids which consist of curcumin, demethoxycurcumin and bisdemethoxycurcmin (2). Curcumin is the main active component of turmeric and the one which gives turmeric its yellow color. It was first introduced by Lampe and Milobedzka in 1910 (2,3). Considering a wide range of pharmacological properties that curcumin offers, numerous studies have investigated its potency as a therapeutic agent in various diseases. The conducted fundamental researches on cell cultures and animal models as well as pilot and clinical trials have provided strong evidence for heath promoting activities of this compound (4). Accordingly, it has been shown that curcumin could play pharmacological roles in various disorders such as autoimmune, cardiovascular, neoplastic, pulmonary, neurodegenerative and metabolic diseases (5). The therapeutic potential of curcumin have been also addressed in arthritis, some particular types of cancer, inflammatory bowel disease, chronic anterior uveitis, and pancreatitis (4). Indeed, several lines of evidence have signified antibacterial, antiviral, and antifungal properties of this compound (6). With regard to its wide array of health benefits and therapeutic roles, a single pathway appears unlikely to account for all these activities. With this concept, studies moved forward to investigate the underlying mechanisms contributing to the heath promoting properties of this compound. According to the conducted researches, it can be hypothesized that a complex interaction between three main events including

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inflammation, oxidative stress, and immunity is likely to contribute to different therapeutic roles of curcumin (7, 8). Thus, in this review, the current knowledge on the anti-inflammatory, antioxidant, and immunomodulatory roles of curcumin is discussed with the hope of using curcumin as a therapeutic agent in future therapeutic regimens in order to not only enhance the efficacy of the treatment, but also to decrease the adverse effects of synthetic chemical drugs.

Immunomodulatory effects

The immune system has evolved to various specialized cells, and soluble molecules that are organized into a number of organs and tissues including bone marrow and thymus as the central lymphoid organs and lymph nodes, spleen as well as mucosal lymphoid tissues, as peripheral ones (9).

The immune response conceptually falls into 2 categories: innate and adaptive immunity. Innate immunity presents a stereotyped rapid response well before the evolution of antigen-specific responses provided by adaptive immunity (10). It is now apparent that curcumin could greatly affect both the innate and adaptive arms of immunity through modulating immune cells' function including neutrophils, macrophages, monocytes, natural killer cells (NK cells), dendritic cells (DCs), T cells, and B cells (11). This chapter provides an overview of the current knowledge on the immunomodulatory effects of curcumin on different principal effectors of immune system.

The activation, proliferation, and clonal expansion of T-lymphocytes occur by their initial encounter with antigens presented by antigen-presenting cells (12). The depletion or induction of lymphocytes proliferation has been frequently used as a criterion in evaluation of immunomodulatory effects of therapeutic agents and curcumin is no exception (13-16). In this view, several studies have investigated the effect of curcumin on proliferation of T-cells both ex-vivo and in-vivo. Some literatures revealed that following the induction of proliferation in T cells by a number of compounds such as phytohemagglutinin (PHA), concanavalin A (Con A), and phorbol-12-myristate-13-acetate (PMA), curcumin treatment could noticeably reduce the proliferation (17). However, contradictory data has been published regarding the anti-proliferative effect of curcumin on the T-lymphocytes, as some studies have signified its inductive effects. In this view, Gao et al. conducted a study presenting the wide-ranging functions of curcumin at different concentrations on murine splenic lymphocytes induced by conconavalin A (Con A), IL-2, or alloantigen. The results showed a rise in proliferation of Con A-induced cells at 6.25 μmol/L concentration of curcumin, while the proliferation decreased when 12.5 μmol/L curcumin was used. Furthermore, suppressed proliferative responses were observed at 25 μmol/L concentration of curcumin. With regard to IL-2 induced cells, curcumin showed an inhibitory dose dependent manner as the suppressive effect of curcumin on proliferation increased along with using higher concentration of this compound ranging from 6.25 to 25 μmol/L. Meanwhile, the proliferation of alloantigen-induced spleen cells suppressed at 30 μmol/L curcumin. It is noteworthy that this inhibitory function of curcumin was shown to be irreversible (18). These data could suggest that the effect of curcumin on proliferation rate of T cells depends on both curcumin concentration and type of mitogen. However, the majority of published data are in favor of its inhibitory effects.

The inhibitory effect of curcumin on other immune cells proliferation has also become evident. Studies have shown that curcumin has suppressive effects on the proliferation of B-cell lymphoma cells. This function of curcumin followed a dose- and time-dependent pattern. Curcumin applied these effects by down-regulating the expression of growth and survival promoting genes including c-MYC, BCL-XL and NFκB (19). Coherently, a study on B-cell disorders and curcumin concluded that early intervention with this compound might delay the progression of early hematological malignancies including smoldering multiple myeloma, monoclonal gammopathy of undetermined significance, and stage 0/1 chronic lymphocytic leukemia and prolong the survival of the patients. Interestingly, they revealed that curcumin causes no long-term toxicities even when it is taken over 5 years (20). In concurrence with this report, Haque et al suggested that curcumin treatment could be effective in treating B cell autoimmune disease and reducing the chance for malignant transformation (21). In addition, it has been reported that curcumin could inhibit in vitro B-cell immortalization with EBV (22).

With regard to macrophages, it has been indicated that pre-incubation of these cells with 10 μM curcumin completely suppressed the generation of superoxide anions, nitrite radical, as well as hydrogen peroxide in vitro. Furthermore, the rats fed with curcumin in addition to their typical diet (containing 8 wt% of coconut oil or cod liver oil or olive oil or peanut oil for 8 weeks) showed lower levels of reactive oxygen species (ROS) in their isolated peritoneal macrophages as compared with controls fed with the oil alone. Generally, it is concluded that administering curcumin in combination with dietary fatty acids reduces ROS generation in macrophages (23). In line with this study, Amano et al showed that liposomes containing curcumin could suppress the macrophages in mice in a selective manner (24). A pathway through which curcumin may exert its suppressive effects on macrophages has been suggested to be NF-κB signaling pathway as it has been observed that this compound diminishes macrophage activation and influenza virus induced-lung inflammation by inhibiting NF-κB pathway (25).

Not only curcumin could affect the proliferation and oxidative function of macrophages, but also it can influence their polarization via inhibiting TLR4-

mediated pathway. A study on atheroprotective activity of curcumin in human acute monocytic leukemia THP-1 cells revealed that curcumin exerts aforementioned effects through its anti-inflammatory and atheroprotective properties (26). To further support the role of curcumin in immunomodulation, studies have found that there is a correlation between anti-inflammatory effects of curcumin and down-regulation of microRNA-155 in both LPS-treated macrophages and mice, suggesting that curcumin may mediate the suppression of LPS-induced inflammatory response through the inhibition of miR-155 (27).

Curcumin has also been shown to induce apoptosis and inhibit proliferation of a number of NK/T-cell lymphoma cell lines through mediating some related genes such as NFκB, Bcl-xL, and cyclin D1. These results showed that curcumin could be used for inducing apoptosis even in chemoresistant lymphoma cell lines namely NK-92 which may become a future therapeutic approach (28). Curcumin is also involved in mediating NK cells function by increasing nitric oxide (NO) generation in NK cells following prolonged treatment and enhancing their cytotoxicity (7,29,30). It is noteworthy that the combined treatment of curcumin and omega-3 fatty acids has shown to increase the NK cell-induced apoptosis of pancreatic cancer cells while curcumin alone could inhibit interferon-γ production (31), presenting the dual function of curcumin which possibly could be highly dependent on its in vivo interactions .

Studies further investigated the effect of curcumin on DC function. Regarding surface molecules expression, curcumin noticeably blocked the expression of CD80, CD86, and MHC class II expression. Impaired production of some proinflammatory cytokines including IL1β, IL6 and tumor necrosis factor (TNF)-α was also observed in curcumin-treated DCs. The phosphorylation of MAPK as well as translocation of NFκB was modulated by curcumin (32). These alterations in DC properties arises the question that whether curcumin modifies the physiological function of DC, for instance its antigen capture ability, or not. As further shown by Kim et al, interestingly, DC cells treated with curcumin showed high efficiency at Ag capturing (32). Furthermore, curcumin could affect DC function by arresting its maturation and inducing a tolerogenic phenotype through promoting the activity of FoxP3+ Tregs (33). The suggested pathways through which curcumin has been shown to suppress DCs activation in mice with experimental colitis are JAK/STAT/SOCS signaling pathways (34). Moreover, It is held that curcumin could be applied as an immune suppressant as it has shown promise in preventing the response of human DC cells to immune stimulants (35).

The discussed data from both ex-vivo and in-vivo studies provide evidence on the inhibitory effects of curcumin on mentioned immune cells' proliferation and suppressing immune responses in some cases which could be beneficial in the treatment of autoimmune diseases. However, it has been shown that curcumin present anti-cancer activities through boosting the immune system. It is now apparent that tumor growth and survival results from the failure of immune surveillance processes in detecting and eliminating the cancer cells. Some factors causing this failure have shown to be low number of effector T cells (CD4+ and CD8+) as well as a shift from Th1-secreted cytokines to Th2 ones, which eventually results in diminishing the activity of cytotoxic T lymphocytes (CTLs) (36). In this regard, studies have shown that curcumin could restore the $CD4^+$ and $CD8^+$ cells population, thereby re-establishing the shift towards a Th1-secreted cytokines again. It is worth noting that the loss of both central and memory T cell was prevented by curcumin (37). Coherently, tumor-bearing mice fed with curcumin showed a significant decrease in their tumor cell number. This reduction followed a dose-dependent pattern. Indeed, curcumin reinstated the decreased immune cell number caused by cancer through preventing thymocytes and splenocytes from apoptosis (38). Curcumin is further involved in eliminating cancer by reducing the T-regulatory cell population, maintaining reactive oxygen and nitrogen production by macrophages, and NK cell cytotoxic activity (30,39,40).

Despite the well-established anti-cancer role of curcumin, the observations regarding immune-suppressive effect of curcumin arises the question that how a compound could be both anti-cancer and immune-suppressive. The discussed findings suggest a dual role for curcumin as both inhibitor and inducer of proliferation in immunity cells. In fact it seems that curcumin shows distinct responses under different circumstances and adopts them according to the body condition. For instance in immunity cell cancers, namely lymphoma, as discussed earlier, curcumin presents inhibitory effects on that particular immune cells proliferation while in other type of cancer it increases the immune cells' proliferation to boost immune responses. However, further research is required to elucidate the exact mechanism or microenvironment condition which results in different responses of curcumin.

Anti-inflammatory effects

Curcumin was found to possess a miraculous power in anti-inflammatory processes. Various experimental and pharmacologic trials have signified its efficacy as an anti-inflammatory agent (41). This property of curcumin has been shown to be mediated through down-regulating the activity of various signaling mediators including down-regulation of COX-2 activity, mitogen-activated and Janus kinases, and inhibiting the generation of TNF-alpha, IL-1, -2, -6, -8, -12, and 5′-Adenosine monophosphate-activated protein kinase (41,42). Recently, remarkable progress has been made in our understanding of the inflammatory mechanisms targeted by curcumin (5,41,43). This chapter addresses the most pivotal mediators affected by this

compound within the anti-inflammatory processes.

To begin with, curcumin has been shown to be a potent blocker of inflammatory-induced NF-κB activation (44). NF-κB is a regulator of most mediators of inflammation ranging from chemokines and cytokines to adhesion molecules, kinases and enzymes (45). Curcumin suppresses NF-κB activation by inhibiting IκBα kinase and AKT (46,47). It is also suggested that curcumin targets NF-κB via its antioxidant activity. In this view, studies have shown that NF-κB DNA-binding activity is induced by oxidative stress, thus, antioxidant activity of curcumin might result in a depletion in NF-κB DNA-binding activity (8,48). Curcumin is also believed to reduce the expression of the NF-κB –regulated gene products including IL-1, IL-6, IL-8, cyclooxygenase-2 (COX-2), 5-LOX, MIP-1α, TNF, adhesion molecules, CXCR-4, c-reactive protein (CRP), etc (49-52). Likewise, COX-2 is believed to be involved in several inflammatory disorders through generating pro-inflammatory prostaglandins (53,54). COX-2 inhibitors have also exhibited potential effects on treating the inflammatory diseases (55). There are inconclusive and contradictory findings regarding the effects of curcumin on COX-2 expression which add ambiguity to explain the underlying mechanisms of anti-inflammatory function of curcumin. Numerous published studies present that curcumin could suppress COX-2 expression (56-58), while others believe that it has a inducible effects (59,60). However, the authors have shed light on this disparity between their findings by explaining that the response of malignant and transformed cells may be different from those of primary cells to curcumin treatment (60). Also, it has been suggested that curcumin with concentration higher than 10 μM leads to suppression of COX-2, contrariwise, it acts as an inducible factor when it is imposed in lower doses (58,60,61). Furthermore, regarding the exact target of curcumin in inhibiting the expression of COX-2, it is shown that curcumin treatment could inhibit the expression of COX-2 at both mRNA and protein levels (60,62).

Besides COX-2, inducible nitric oxide synthase (iNOS) is also known to be implicated in inflammatory responses (63). Indeed, iNOS is reported to be another target for curcumin (64). iNOS results in NO generation, a well-known pro-inflammatory mediator (65). Moreover, published studies have demonstrated that iNOS applies its anti-inflammatory function through the regulation of COX-2 and, thus, generating prostaglandins (66). Studies have shown that curcumin acts as an anti-inflammatory agent through inhibiting the NO generation as well as iNOS expression at both protein and mRNA levels (67,68). Moreover, it has been shown that curcumin might downregulate the iNOS gene via suppression of c-Jun/AP-1 activation (68).

The other target of curcumin in reducing inflammation is believed to be TNF. TNF has shown to exert pro-inflammatory effects through TNF receptor 2 (69). It has been suggested that curcumin could modulate the TNF-α-associated inflammatory pathways (70). Some publications have shown that curcumin inhibits TNF production, but still, the exact underlying signaling are unclear (51,70) . Nevertheless, there are several possibilities regarding the TNF-α regulation by curcumin as presented by both in vitro and animal studies. For instance, it has been reported that curcumin could negatively regulate pro-inflammatory transcription factors including NF-kB, STAT proteins, and activator protein-1, thereby modulating TNF-α production (71). The interruption of signaling between TNF-α and its receptor by curcumin direct binding has also been suggested as another mechanism through which curcumin could suppress the inflammation induced by this cytokine (72).

In accordance with the investigations on inflammatory signaling mediators which curcumin targets, experimental studies have further proved the anti-inflammatory activity of this compound. In this aspect, animal studies on the effect of curcumin on inflammation have shown that administering curcumin could also inhibit in-vivo inflammation. In this regard, a study conducted on rat model of streptococcal cell wall-induced rheumatoid arthritis showed that injection of an extract containing curcuminoids prior to induction of arthritis prevented joint inflammation, remarkably (73). Curcumin also reduced inflammation in rat models of pancreatitis through suppressing NF-κB and AP-1 as well as decreasing TNF-a, IL-6, and iNOS in the pancreas, thereby an improvement in disease severity was observed (74).

Taken together, the discussed publications provide strong evidence for the anti-inflammatory properties of curcumin which might become as a simpler answer, in comparison with current therapies, to various inflammatory diseases.

Antioxidant effects

Curcumin is known for its antioxidant and radical scavenging properties. The unique chemical structure of this compound including its carbon–carbon double bonds, B-diketo group, and phenyl rings with hydroxyl and methoxy substituents has been proven to attribute to its antioxidant activity (8,75). Scientists believe that the superb antioxidant features of curcumin are mainly due to its H-atom donation from the phenolic group (76).

In recent years, there has been a particular interest in investigating scavenging properties of curcumin. Studies have shown that curcumin could scavenge free radicals efficiently (76,77). Besides, evidence demonstrated that curcumin is mainly involved in scavenging of these radicals in peroxidation processes. Therefore, possessing a great potency to inhibit lipid peroxidation, curcumin could protect cell membrane from oxidative damage by positioning itself within the cell membrane (8,75). In this scenario, studies indicated that curcumin

inhibits peroxidation mainly through its iron binding capacity (76). Curcumin also is considered as a potential antioxidant against hydrogen peroxide and superoxide radical generation (76).

The antioxidant properties of curcumin set up essential protective tasks for this compound specifically in reproductive system. For instance, it is well-understood that an appropriate balance between oxidant and antioxidant is a crucial factor for efficient performance of human reproductive system (78). Studies have shown that curcumin could protect structural integrity and functional activity of the spermatozoa particularly when oxidative damage to the germ cells is elevated. It could be explained by its phenol group which prevents oxidative cellular damage (79,80). In accordance with this data earlier studies have shown that curcumin could have ameliorative effects on the both antioxidant status and activity of reproductive cells and tissues in mice treated with metronidazole (81). Considering more studies in this aspect, studies have reported that the balance between oxidant and antioxidant is often altered following cryopreservation of semen. Curcumin has been shown to preserve this balance by its antioxidant capacity (82). The stabilization of the total antioxidant equilibrium mediated by curcumin also results in protection of DNA integrity and viability in rat spermatozoa (82). Furthermore, it has been shown that treatment of spermatozoa with curcumin results in preservation of its motion, and preserves its mitochondrial as well as antioxidant characteristics, which are characterized by elevated superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione (GSH) activities following curcumin treatment (83).

Curcumin was also shown to have potential effects on inhibiting oxidative damages caused by chronic stress in vital organs including brain, liver and kidney. It has been proven that curcumin plays this role through maintaining the SOD and GPx activity as well as reversing the stress-induced inhibition of CAT. These functions of curcumin may eventually result in a reduction in lipid peroxidation and, thus, ameliorate the detrimental effect of chronic stress on tissues (84).

Moreover, since oxidative stress is implicated in most of the neurodegenerative diseases, studies have investigated the possible protective effect of curcumin as an antioxidant, on astrocytes. In this regard, Daverey et al showed that curcumin not only inhibits the oxidative stress and its following adverse effects, but also protects astrocytes. Curcumin exhibited its antioxidant activity through ameliorating astrogliosis markers (GFAP and vimentin) and suppressing upregulation of Prdx6 induced by oxidative stress (85). In addition, treatment with curcumin results in recovery of the damaged mitochondria caused by oxidative stress (85). Furthermore, Wu et al demonstrated that curcumin treatment elevated both protein expression and enzyme activity of thioredoxin in rat cerebral cortical neurons, thus preserving them against cell injury (86). The antioxidant activity of this compound can be further confirmed by the study conducted by Suryanarayana et al who investigated the effect of curcumin administration on streptozotocin-induced hyperglycemic rat, as they showed elevated protein carbonyls, lipid peroxidation and altered activities of enzymatic antioxidant. Subsequently, administering curcumin and turmeric inhibits oxidative stress and reversed the altered balance (87).

It is worth noting that as discussed in the former section curcumin treatment suppressed the generation of superoxide anions, nitrite radical, as well as hydrogen peroxide in macrophages in vitro. This fact could be due to the antioxidant effects of curcumin. However, as macrophages use these oxidative mediators to combat the invader we could be facing a paradigm shift in how antioxidant activity of this compound should be viewed in inflammatory conditions particularly in terms of macrophages function. Beside this fact, in contrast to the traditional view of oxidative mediators, as a cause of tissue destruction and mediating inflammation, scientists have suggested that ROS are implicated in diminishing the inflammatory response. ROS also have been reported to be beneficial in autoimmune conditions (88). However, these hypotheses demand further support and are yet to be adequately understood since there are few studies discussing these issues, thus, it remains inconclusive.

Conclusion

In view of the discussed findings, future therapeutic approaches could rely on the ability of curcumin to prevent the oxidative stress, inflammation and immunomodulatory disorders. The literatures support the candidacy of this compound as a possible prospective natural drug and raise the possibility of recruiting curcumin in future therapeutic regimens. However, Additional studies and further investigations are needed to provide a better comprehension of the role of curcumin in prevention as well as treatment of the aforementioned disorders for better management of patients affected by these conditions. Moreover, the exact role of this compound as an antioxidant, anti-inflammatory and immunomodulatory agent should be well distinguished.

Authors' contributions

All the authors contributed to data collection and preparation of the manuscript. The first draft was prepared by NB. All authors read the final version and confirmed for the publication.

Conflict of interest

Authors declare there is not any conflict of interest.

Ethical considerations

Ethical issues including text plagiarism, misconduct, manipulation or appropriation, data fabrication,

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